UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,997	04/09/2007	Stephen Gillies	3287.1025-000 (ANTBH/P317	4525

21005 7590 05/25/2010

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
05/25/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,997	GILLIES ET AL.	
	Examiner	Art Unit	
	DAVID J. BLANCHARD	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-34,43,44,47-50 and 53-58* is/are pending in the application.

4a) Of the above claim(s) *47-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-34,43,44 and 53-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1 Claims 1, 4-34, 43-44, 47-50 and 53-58 are pending.

Claims 2-3, 35-42, 45-46 and 51-52 are cancelled.

Claims 1, 8-9, 11-15, 18-22, 24 and 29-34 have been amended.

Claims 53-58 have been added.

2. Claims 47-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1, 4-34, 43-44 and 53-58 are under consideration.

Objections/rejections Withdrawn

4. The objections to claims 2, 9 and 33 are withdrawn in view of the amendments to the claims and the cancellation of claim 2.

5. The rejection of claim 19 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "derived" is withdrawn in view of the amendments to the claim.

6. The rejection of claims 11-13 and 30-33 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "a polypeptide of SEQ ID NO…" is withdrawn in view of the amendments to the claims.

7. The rejection of claims 2-3 and 45 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the cancellation of the claims.

8. The rejection of claims 2-3 and 45 under 35 U.S.C. 103(a) as being unpatentable over Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) in view of Gillies et al [a] (The Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) and Gillies et al [b] (US Patent 6,838,260 B2, priority to 12/8/1997) is withdrawn in view of the cancellation of the claims.

9. The rejection of claims 2-3 and 45 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 7,226,998 in view of Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) and in

view of Gillies et al [a] (The Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) is withdrawn in view of the cancellation of the claims.

10. The rejection of claims 2-3 and 45 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 6-8 of U.S. Patent No. 6,838,260 B2 in view of Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) and in view of Gillies et al [a] (The Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) is withdrawn in view of the cancellation of the claims.

11. The rejection of claims 2-3 and 45 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7 and 10 of U.S. Patent No. 6,617,135 B1 in view of Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) and in view of Gillies et al [a] (The Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) is withdrawn in view of the cancellation of the claims.

Objections/Rejections Maintained and New Grounds of Rejections

12. The objection to the specification at pg. 5 as disclosing the BC1 antibody as a human antibody and as disclosing a compound comprising a human BC1 heavy chain variable region of SEQ ID NO:1 and a human BC1 light chain variable region of SEQ ID NO:2 at pp. 8-9 of the specification is maintained.

The reply filed 2/18/2010 states that paragraphs 0017 and 0020 are amended to clarify that the antibody known as BC1 is a murine antibody. Applicants' reply has been fully considered but is not found persuasive. As set forth in the previous office action, while it is clear that BC1 is a murine monoclonal antibody, the reply does not fully address the issue where the specification references BC1 as a human antibody (specification at pg. 5, lines 8-15) or as comprising a human BC1 heavy chain variable region of SEQ ID NO:1 and a human BC1 light chain variable region of SEQ ID NO:2 (see pg. 8 of specification). While one skilled in the art would recognize that a humanized BC1 antibody could be produced from the murine monoclonal BC1 antibody, the disclosure of a human BC1 antibody is inconsistent with the disclosure and prior art which defines BC1 as a murine monoclonal antibody. Again, the BC1 antibody is a

murine antibody and will never be a human antibody or comprise human heavy and light chain variable regions.

Appropriate correction is required.

13. The rejection of claim 15 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "FAB-like molecules, such as..." is maintained.

The reply filed 2/18/2010 states that the claim has been amended to remove the recitation "such as" and applicant submits that the term "Fab-like molecule is a term of art accepted by those of ordinary skill. Applicant supplies Exhibit A (Better et al) wherein the authors explain that the susceptibility of different antibodies to proteolytic cleavage differs and preparations can be heterogeneous and since it is cumbersome to describe all possible ways in which antibodies are proteolytically cleaved, the term "FAB-like" is used. Applicants' arguments and evidence have been fully considered but are not found persuasive. Better et al supplied by applicant as Exhibit A merely indicates that proteolytic digestion of different antibodies results in different ratios of digested Fab' to whole antibody, since different antibodies have different susceptibility to proteolytic digestion. Thus, the resultant structures disclosed by Better et al either a Fab or whole antibody, whereas the term "FAB-like molecule" is relative in nature and is not defined by the claim and embraces Fab molecules with amino acid substitutions, insertions, or deletions, chemically derivatized molecules, or even mimetics, e.g., undefined structures that function equivalently (e.g., bind antigen). It is reiterated that term "FAB-like molecules" is not defined by the claims; the specification does not provide a standard for ascertaining the direction, requisite degree or endpoint, and one of ordinary skill in the art would not reasonably be apprised of the metes and bounds of the invention and the rejection is maintained. Amending the claim to recite wherein the antigen-binding fragment thereof (of base claim 14) is selected from the group consisting of Fab, F(ab')2, Fv molecules, disulphide-linked Fv molecules and scFv molecules would clearly define the antigen-binding fragment and would be readily recognized by those skilled in the art such that one could determine infringing subject matter.

14. The rejection of claims 5-6, 8-10 and 20 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of the evidence that antibody BC1 is publicly available is maintained.

The reply filed 2/18/2010 states that the instant specification provides evidence that the BC1 murine monoclonal antibody is available to the public because (1) it has been described in a printed publication (EP 0 344 134 B) and (2) the hybridoma lines producing this antibody have been deposited with the European Collection of Animal Cell Cultures and are publicly accessible (Accession No. 88042101). Applicants' arguments have been fully considered but are not found persuasive. Applicant is reminded that the mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. *Ex parte Hildebrand*, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990). Further, a search of the Accession No. 88042101 from the European Collection of Animal Cell Cultures web site did not yield any results. Applicant has not made of record any of the facts and circumstances surrounding their access to the material at issue from the depository, nor is there any evidence as to the depository's policy regarding the material. Further, there is no assurance that the depository would have allowed unlimited access to the material if the instant application matures into a patent.

Applicant also states that because BC1's antigen is known and because methods of antibody production have been known for many decades, it is merely a matter of routine experimentation for one of ordinary skill in the art to obtain the BC1 antibody. Applicants' arguments have been fully considered but are not found persuasive. As set forth in the previous

Office Action, exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive a monoclonal antibody and hybridoma identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies and hybridomas.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibody BC1, a suitable deposit is required for patent purposes, evidence of public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody, is required.

Additionally, applicant is reminded that Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed. See MPEP 2406 and 37 CFR 1.804(b).

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

15. The rejection of claims 1, 4-29, 34, 43-44 and now applied to newly added claim 58 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description

requirement is maintained. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The reply filed 2/18/2010 references Example 13 of the written description guidelines (www.uspto.gov/web/menu/written.pdf) and states that claim 1 defines a compound that includes a monoclonal antibody, or fragment or variant thereof, capable of binding to a specific antigen. Applicant states that production of antibodies against a well-characterized antigen was conventional. The derivation of functional fragments or variants of an antibody was also conventional and applicant submits that the entire genus of the target specific portion of the product of claim 1 is fully described. With respect to the effector portion that is IL-12, or a functional fragment or variant thereof, Applicant states that IL-12 is a known protein studied for decades and testing for IL-12 activity is also a matter of routine experimentation. Thus, just as "[a] person of skill in the art would not consider knowledge of the amino acid sequence of the variable regions critical for purposes of assessing possession of the antibody[,]" a person of ordinary skill in the art would not consider knowledge of the amino acid sequence of various IL-12 variants or fragments critical in possession. Applicants' arguments have been fully considered but are not found persuasive. Applicants' reference to example 13 is misplaced in that Example 13 of the written description guidelines is limited to an antibody to a single protein, however, unlike the instant claims, Example 13 does not address the genus of antibody variants. While the disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen, this does not provide adequate written description of a genus of antibody variants. *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (holding there is a lack of written descriptive support for an antibody defined by its binding affinity to an antigen that itself was not adequately described). In contrast to Example 13 of the written description guidelines, which are not drawn to protein variants, the examiner points out that Example 9 of the written description guidelines is directed to protein variants and as such is more relevant to the instantly claimed antibody variants and IL-12 functional fragments and variants. Similar to Example 9, and as set forth in the previous office action since the disclosure does not describe the common attributes or structural

characteristics that identify members of the genus, and because the genus is highly variant, the function of the binding oncofetal fibronectin and stimulating a Th1 immune response in a mammal host alone are insufficient to describe the genus of an antibody "variant thereof" and an IL-12 "functional fragment or variant thereof" that function equivalently. The recitations "variant thereof" and "functional fragment and variant thereof" does not convey a common structure nor a common function. As such, generic polypeptide sequences that are unrelated via structure and function are highly variant and not conveyed by way of written description by the specification at the time of filing. As such the specification lacks written description for the highly variant genus of single function antibody variants ("variant thereof") and single function IL-12 functional fragments and variants thereof and one skilled in the art would not recognize that applicants had possession of the genus of claimed antibody variants which retain binding specificity for oncofetal fibronectin, nor possession of the claimed IL-12 functional fragments and variants thereof as instantly claimed.

While newly added claim 58 recites the sequence of the IL-12 domains of the effector portion, claim 58 also recites antibody variants ("variant thereof"), which lacks adequate written description a set forth in the original rejection and reiterated above.

Further, applicants' arguments that one skilled in the art could routinely screen for antibodies capable of binding to a specific antigen and could test for IL-12 activity (e.g., stimulation of a Th1 immune response) goes more towards enablement and not the issue of written description. Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991) (While acknowledging that some of its cases concerning the written description requirement and the enablement requirement are confusing, the Federal Circuit reaffirmed that under 35 U.S.C. 112, first paragraph, the written description requirement is separate and distinct from the enablement requirement and gave an example thereof.). An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges

would be enabling for formulations falling within the description but would not describe any specific formulation).

"It is not a question whether one skilled in the art might be able to construct the patentee's device from the teachings of the disclosure of the application. Rather, it is a question whether the application necessarily discloses that particular device." *Id.* at 536. *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991), with respect to the first paragraph of §112 the severability of its "written description" provision from its enablement ("make and use") provision was recognized by this court's predecessor, the Court of Customs and Patent Appeals, as early as *In re Ruschig,* 379 F.2d 990, 154 USPQ 118 (CCPA 1967). Although the appellants in that case had presumed that the rejection appealed from was based on the enablement requirement of §112, *id.* at 995, 154 USPQ at 123, the court disagreed: the question is not whether [one skilled in the art] would be so enabled but whether the specification discloses the compound to him, specifically, *as something appellants actually invented.* ... If [the rejection is] based on section 112, it is on the requirement thereof that "The specification shall contain a written description *of the invention* * * *." (Emphasis ours.) *Id.* at 995-96, 154 USPQ at 123 (first emphasis added). The issue, as the court saw it, was one of fact: "Does the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed]?" *Id.* at 996, 154 USPQ at 123. In a 1971 case again involving chemical subject matter, the court expressly stated that "it is possible for a specification to *enable* the practice of an invention as broadly as it is claimed, and still not *describe* that invention." *In re DiLeone,* 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971) (emphasis added). As an example, the court posited the situation "where the specification discusses *only* compound A and contains *no* broadening language of any kind. This might very well enable one skilled in the art to make and use compounds B and C; yet the class consisting of A, B and C has not been described." *Id.* at 1405 n.1, 168 USPQ 593 n.1 (emphases in original). *See also In re Ahlbrecht,* 435 F.2d 908, 911, 168 USPQ 293, 296 (CCPA 1971) (although disclosure of parent application may have *enabled* production of claimed esters having 2-12 methylene groups, it only *described* esters having 3-12 methylene groups).

Therefore, only a monoclonal antibody and fragments thereof (e.g., Fab, F(ab')2, Fv, dsFv, scFv) that bind oncofetal fibronectin and interleukin-12, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph and the rejection is maintained.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. The rejection of claims 1, 4-7, 11-27, 34, 43-44 and now applied to newly added claims 53-54 and 57-58 under 35 U.S.C. 103(a) as being unpatentable over Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) in view of Gillies et al [a] (The

Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) and Gillies et al [b] (US Patent 6,838,260 B2, priority to 12/8/1997) is maintained.

The applied reference (Gillies et al [b]) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Mariani et al teach monoclonal antibody BC1 that binds human oncofetal fibronectin, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues and radiolabeled BC-1 showed favorable tumor targeting *in vivo* (see entire document, particularly pp. 2485, 2487-2489). Mariani et al do not specifically teach BC1-IL-12 fusion proteins, humanized BC1-IL-12 or scFv-IL-12 (e.g., single-chain-IL-12) fusion proteins, or wherein the BC1 comprises the heavy chain variable region of SEQ ID NO:1 and the light chain variable region of SEQ ID NO:2, or wherein IL-12 is human, wherein the IL-12p35 domain is conjugated to the IL-12p40 domain by a disulfide bond or a composition comprising the BC1-IL-12 fusion protein and a pharmaceutically acceptable carrier. These deficiencies are made up for in the teachings of Gillies et al [a] and Gillies et al [b].

Gillies et al [a] teach antitumor antibody-IL-12 fusion proteins comprising human p35 and p40 domains that induce active antitumor immune responses within the tumor microenvironment and provides an important alternative to systemic IL-12 administration or gene therapy for increasing its therapeutic index, wherein the antibody-IL-12 fusion proteins

include whole antibody-IL-12, humanized antibody-IL-12 and scFv-IL-12 (see entire document, particularly pp. 6195-6196 and 6200-6202).

Gillies et al [b] also teach antibody-IL-12 fusion proteins, including whole antibody-IL-12, humanized antibody-IL-12 and scFv-IL-12 for cancer immunotherapy, wherein IL-12 comprises human p35 and p40 domains and may be linked by a disulfide bond (e.g., Fig. 1B) and Gillies et al teach the intravenous administration of the antibody-IL-12 fusion proteins in PBS buffer (e.g., pharmaceutically acceptable carrier), which unlike treatment with systemic IL-12, antibody-IL-12 fusion protein therapy can eradicate established metastatic colon carcinoma in a murine model (see entire document, particularly cols. 2-3, 5-6, Examples 5-8 and Figs. 1 and 6).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of Mariani et al and Gillies et al [a] and Gillies et al [b] because Mariani et al teach monoclonal antibody BC1 that binds human oncofetal fibronectin, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues and radiolabeled BC-1 showed favorable tumor targeting *in vivo* and Gillies et al [a] teach antitumor antibody-IL-12 fusion proteins comprising human p35 and p40 domains that induce active antitumor immune responses within the tumor microenvironment and provides an important alternative to systemic IL-12 administration or gene therapy for increasing its therapeutic index, wherein the antibody-IL-12 fusion proteins include whole antibody-IL-12, humanized antibody-IL-12 and scFv-IL-12 and Gillies et al [b] also teach antibody-IL-12 fusion proteins, including whole antibody-IL-12, humanized antibody-IL-12 and scFv-IL-12 for cancer immunotherapy, wherein IL-12 comprises human p35 and p40 domains and may be linked by a disulfide bond (e.g., Fig. 1B) and Gillies et al [b] teach that unlike treatment with systemic IL-12, intravenous administration of antibody-IL-12 fusion proteins in PBS buffer (e.g., pharmaceutically

acceptable carrier), can eradicate established metastatic colon carcinoma in a murine model. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated by the goal of increasing the therapeutic index of IL-12 by targeting IL-12 within the tumor microenvironment for inducing enhanced antitumor immune responses unlike those induced by systemic IL-12 and one of ordinary skill in the art would have been motivated to use the BC1 antibody or antigen-binding region thereof (e.g., Fab. F(ab')2, scFv) and humanized BC1 antibodies that target human oncofetal fibronectin, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues and radiolabeled BC1 showed favorable tumor targeting *in vivo*. Thus, there would have been advantages to targeting human IL-12 to the tumor microenvironment and the BC1 antibody or antigen binding fragments thereof target the human oncofetal fibronectin antigen, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of Mariani et al and Gillies et al [a] and Gillies et al [b]. Further, as evidenced by the specification at pp. 4-5, the BC1-IL-12 fusion proteins Mariani et al and Gillies et al [a] and Gillies et al [b] would necessarily bind to human oncofetal fibronectin via a site on repeat 7, outside the ED-B domain and would necessarily comprise the BC1 heavy chain variable region sequence of SEQ ID NO:1 and the BC1 light chain variable region sequence of SEQ ID NO:2. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. The rejection of claims 1, 5-6 and 8-10 under 35 U.S.C. 103(a) as being unpatentable over Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) in view of Gillies et al [a] (The Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) and Gillies et al [b] (US Patent 6,838,260 B2, priority to 12/8/1997) as applied to claims 1-7, 11-27, 34 and 43-45 above, and further in view of Schier et al (Journal of Molecular Biology, 263:551-567, 1996) is maintained.

Mariani et al in view of Gillies et al [a] and Gillies et al [b] have been described supra. Mariani et al in view of Gillies et al [a] and Gillies et al [b] do not specifically teach wherein the BC1-IL-12 fusion proteins bind to oncofetal fibronectin at least 2-fold or at least 10-fold tighter than parental antibody BC1. This deficiency is made up for in the teachings of Schier et al.

Schier et al teach methods for producing a higher affinity antitumor antibody by restricting mutagenesis to the CDRs located at the center of the antibody combining site, which resulted in certain mutant antibodies having a 16-fold increase and a 1230-fold increase in affinity and according to Schier et al higher affinity antibodies with enhanced binding kinetics offer the possibility of significantly greater quantitative tumor retention (see entire document, particularly abstract, 553-554, 556 and Tables 2-4).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced modified BC1-IL-12 fusion proteins having increased affinities for human oncofetal fibronectin for therapeutic benefit in cancer patients in view of Mariani et al and Gillies et al [a] and Gillies et al [b] and Schier et al because Schier et al teach a methods for producing a higher affinity antitumor antibody by restricting mutagenesis to the CDRs located at the center of the antibody combining site, which resulted in certain mutant antibodies having a 16-fold increase and a 1230-fold increase in affinity and according to Schier et al higher affinity antibodies with enhanced binding kinetics offer the possibility of significantly greater quantitative tumor retention. Thus, there would have been an advantage to modifying the BC1 antigen-binding domain according to the teachings of

Shier et al for producing high affinity BC1 antibodies having greater tumor retention for use in the BC1-IL-12 fusion proteins of Mariani et al and Gillies et al [a] and Gillies et al [b].

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

19. The rejection of claims 1, 26-29 and now applied to newly added claims 55-56 under 35 U.S.C. 103(a) as being unpatentable over Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) in view of Gillies et al [a] (The Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) and Gillies et al [b] (US Patent 6,838,260 B2, priority to 12/8/1997) as applied to claims 1-7, 11-27, 34 and 43-45 above, and further in view of Gillies SD [c] (WO 02/79232 A2, published 10/10/2002) is maintained.

Mariani et al in view of Gillies et al [a] and Gillies et al [b] have been described supra. Mariani et al in view of Gillies et al [a] and Gillies et al [b] do not specifically teach wherein the immunoglobulin heavy chain and the IL-12 (effector portion) are joined via a mutated linker sequence that comprises or consists of the amino acid sequence ATATPGAA. This deficiency is made up for in the teachings of Gillies [c].

Gillies [c] teaches the modification of amino acid residues at the junction of an antibody-cytokine fusion protein to reduce immunogenicity by elimination of MHC class II binding motifs, wherein the junction sequence LSLSPGKAP is changed to ATTAPGAAP that was incapable of binding to any human MHC class II with an affinity high enough to result in immunogenicity (see entire document, particularly pg. 16 and SEQ ID NO:18).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains fused to the BC1 antibodies via the junction sequence ATATPGAAP for therapeutic benefit in cancer patients in view of Mariani et al and Gillies et al [a] and Gillies et al [b] and Gillies [c] because Gillies [c] teaches the modification of amino acid residues at the junction of an antibody-cytokine fusion protein to reduce immunogenicity by elimination of MHC class II binding motifs, wherein the junction

sequence LSLSPGKAP is changed to ATTAPGAAP that was incapable of binding to any human MHC class II with an affinity high enough to result in immunogenicity. Thus, there would have been an advantage to using the junction peptide ATTAPGAAP of Gillies [c] to fuse the BC1 antibodies to the human IL-12p35 and IL-12p40 domains fused as taught by Mariani et al and Gillies et al [a] and Gillies et al [b].

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

The reply filed 2/18/2010 states that one of ordinary skill in the art would not have been motivated to target IL-12 to a non-ED-B domain and targeting the non-EB-D region confers unexpected advantages including reduced IL-12 bioactivity in PBMC assays and which allows for an increased maximum tolerated dose and BC1 targeted IL-12 suggests a more favorable therapeutic index as well as postulating a longer serum half-life and a resultant better efficacy in the clinic. Applicants' arguments and evidence have been fully considered but are not found persuasive. Applicants' arguments overlook the teachings of Mariani et al and reviews the obviousness inquiry form the perspective of whether one of ordinary skill in the art would have been motivated to target a region of oncofetal fibronectin that is outside of the ED-B region. However Mariani et al already teaches the BC1 monoclonal antibody and demonstrated radiolabeled BC-1 showed favorable tumor targeting *in vivo*. Thus, since the BC1 monoclonal antibody was already known and shown to have favorable tumor targeting the appropriate question is whether or not one of ordinary skill in the art would have been motivated to target IL-12 to tumors using the BC1 antibody. As set forth in the above rejections, Gillies et al [a] and [b] teach antibody-IL-12 fusion proteins increase the therapeutic index of IL-12 by targeting IL-12 within the tumor microenvironment for inducing enhanced antitumor immune responses unlike those induced by systemic IL-12. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated by the goal of increasing the therapeutic index of IL-12 by targeting IL-12 within the tumor microenvironment for inducing enhanced antitumor immune responses unlike those induced by systemic IL-12 and one of ordinary skill in the art would have been motivated to use the BC1 antibody or antigen-binding region thereof (e.g., Fab.

F(ab')2, scFv) and humanized BC1 antibodies that target human oncofetal fibronectin, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues and radiolabeled BC1 showed favorable tumor targeting *in vivo*.

With respect to the unexpected advantages of the BC1-IL-12 fusion proteins, these advantages would have been a consequence of following the teachings and suggestions of the cited prior art references. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979) (Claims were directed to grooved carbon disc brakes wherein the grooves were provided to vent steam or vapor during a braking action. A prior art reference taught noncarbon disc brakes which were grooved for the purpose of cooling the faces of the braking members and eliminating dust. The court held the prior art references when combined would overcome the problems of dust and overheating solved by the prior art and would inherently overcome the steam or vapor cause of the problem relied upon for patentability by applicants. Granting a patent on the discovery of an unknown but inherent function (here venting steam or vapor) "would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art." 596 F.2d at 1022, 201 USPQ at 661.). Additionally, Applicant is reminded that the submission of objective evidence of patentability does not mandate a conclusion of patentability in and of itself. *In re Chupp*, 816 F.2d 643, 2 USPQ2d 1437 (Fed. Cir. 1987). Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of a *prima facie* case was reached, not against the conclusion itself. *In re Eli Lilly*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990). In other words, each piece of rebuttal evidence should not be evaluated for its ability to knockdown the *prima facie* case. All of the competent rebuttal evidence taken as a whole should be weighed against the evidence supporting the *prima facie* case. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984). Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the

objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness. *Newell Cos. v. Kenney Mfg. Co.,* 864 F.2d 757, 769, 9 USPQ2d 1417, 1427 (Fed. Cir. 1988).

Accordingly, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejections are maintained.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. The rejection of claims 1, 4-7, 11-27, 34, 43-44 and now applied to newly added claims 53-54 and 57-58 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 7,226,998 in view of Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) and in view of Gillies et al [a] (The Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) is maintained. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1-8 of U.S. Patent No. 7,226,998 are drawn to a fusion comprising an immunoglobulin (Ig) moiety linked by a peptide bond to the p35 subunit of IL-12, the p35 subunit of IL-12 being linked to the p40 subunit of IL-12, wherein the Ig moiety comprises a single-chain Fv (scFv) antibody, the scFv antibody, wherein the Ig light chain variable region is N-terminal relative to the Ig heavy chain variable region, wherein the p35 subunit of IL-12 and the p40 subunit of IL-12 are linked by a disulfide bond, wherein the p35 subunit of IL-12 is linked to the amino terminus of the Ig moiety or Ig heavy chain, wherein the Ig moiety has antigen-binding specificity and a fusion protein comprising a single-chain Fv (scFv) antibody linked by a peptide bond to the p35 subunit of IL-12, the p35 subunit of IL- 12 being linked to the p40 subunit of IL-12, wherein the scFv antibody comprises an Ig heavy chain variable region linked by a linker sequence to an Ig light chain variable region. Claims 1-8 of U.S. Patent No. 7,226,998 do not specifically teach wherein the scFv antibody comprises the heavy and light chain variable regions of the BC1 antibody or wherein the antibody is the BC1 antibody, or a humanized BC1 antibody. These deficiencies are made up for in the teachings of Mariani et al and Gillies et al [a].

Mariani et al have been described supra.

Gillies et al [a] have been described supra.

The claims in the instant application are obvious variants of claims 1-8 of U.S. Patent No. 7,226,998 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of claims 1-8 of U.S. Patent No. 7,226,998 and Mariani et al and Gillies et al [a].

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of claims 1-8 of U.S. Patent No. 7,226,998 and Mariani et al and Gillies et al [a] because Mariani et al teach monoclonal antibody BC1 that binds human oncofetal fibronectin, which has extremely

restricted distribution in normal adult tissues and is highly expressed in tumor tissues and radiolabeled BC-1 showed favorable tumor targeting *in vivo* and Gillies et al [a] teach antitumor antibody-IL-12 fusion proteins comprising human p35 and p40 domains that induce active antitumor immune responses within the tumor microenvironment and provides an important alternative to systemic IL-12 administration or gene therapy for increasing its therapeutic index, wherein the antibody-IL-12 fusion proteins include whole antibody-IL-12, humanized antibody-IL-12 and scFv-IL-12. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to increase the therapeutic index of IL-12 by targeting IL-12 within the tumor microenvironment for inducing antitumor immune responses and one of ordinary skill in the art would have been motivated to target human oncofetal fibronectin, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues using the BC1 antibody or antigen-binding region thereof (e.g., scFv), or humanized BC1 antibodies. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of claims 1-8 of U.S. Patent No. 7,226,998 and Mariani et al and Gillies et al [a].

Claims 1, 4-7, 11-27, 34, 43-44, 53-54 and 57-58 are directed to an invention not patentably distinct from claims 1-8 of commonly assigned U.S. Patent No. 7,226,998. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 7,226,998, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

22. The rejection of claims 1, 4-7, 11-27, 34, 43-44 and now applied to newly added claims 53-54 and 57-58 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 6-8 of U.S. Patent No. 6,838,260 B2 in view of Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) and in view of Gillies et al [a] (The Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) is maintained. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1-3 and 6-8 of U.S. Patent No. 6,838,260 B2 are drawn to a heterodimeric fusion protein comprising a first and a second chimeric chain, said first chimeric chain comprising a portion of an Ig heavy chain linked by a peptide bond to a p35 subunit of IL-12 said second chimeric chain comprising a portion of an Ig heavy chain linked by a peptide bond to a p40 subunit of IL-12, said first and second chimeric chains being linked by a disulfide bond, and a fusion protein comprising a first chimeric Ig chain comprising a portion of an Ig heavy chain linked by a peptide bond to a p40 subunit of IL-12, said p40 subunit of IL-12 being linked to a p35 subunit of IL-12 and further comprising a second chimeric Ig chain comprising a portion of an Ig heavy chain linked by a peptide bond to a p40 subunit of IL-12, said p40 subunit of IL-12 being linked to a p35 subunit of IL-12 or vice versa, said first and second chimeric chains being linked by a disulfide bond. Claims 1-3 and 6-8 of U.S. Patent No. 6,838,260 B2 do not specifically teach wherein the antibody comprises the heavy and light chain variable regions of the BC1 antibody or wherein the antibody is the BC1 antibody, or a humanized BC1 antibody. These deficiencies are made up for in the teachings of Mariani et al and Gillies et al [a].

Mariani et al have been described supra.

Gillies et al [a] have been described supra.

The claims in the instant application are obvious variants of claims 1-3 and 6-8 of U.S. Patent No. 6,838,260 B2 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of claims 1-3 and 6-8 of U.S. Patent No. 6,838,260 B2 and Mariani et al and Gillies et al [a].

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of claims 1-3 and 6-8 of U.S. Patent No. 6,838,260 B2 and Mariani et al and Gillies et al [a] because Mariani et al teach monoclonal antibody BC1 that binds human oncofetal fibronectin, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues and radiolabeled BC-1 showed favorable tumor targeting *in vivo* and Gillies et al [a] teach antitumor antibody-IL-12 fusion proteins comprising human p35 and p40 domains that induce active antitumor immune responses within the tumor microenvironment and provides an important alternative to systemic IL-12 administration or gene therapy for increasing its therapeutic index, wherein the antibody-IL-12 fusion proteins include whole antibody-IL-12, humanized antibody-IL-12 and scFv-IL-12. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to increase the therapeutic index of IL-12 by targeting IL-12 within the tumor microenvironment for inducing antitumor immune responses and one of ordinary skill in the art would have been motivated to target human oncofetal fibronectin, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues using the BC1 antibody or antigen-binding region thereof (e.g., scFv), or humanized BC1 antibodies. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-

12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of claims 1-3 and 6-8 of U.S. Patent No. 6,838,260 B2 and Mariani et al and Gillies et al [a].

Claims 1, 4-7, 11-27, 34, 43-44, 53-54 and 57-58 are directed to an invention not patentably distinct from claims 1-8 of commonly assigned U.S. Patent No. 6,838,260 B2. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,838,260 B2, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

23. The rejection of claims 1, 4-7, 11-27, 34, 43-44 and now applied to newly added claims 53-54 and 57-58 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7 and 10 of U.S. Patent No. 6,617,135 B1 in view of Mariani et al (Cancer, 80(12 Suppl.):2484-2489, 1997, cited on PTO-892 mailed 4/27/09) and in view of Gillies et al [a] (The Journal of Immunology, 160(12):6195-6203, 1998, IDS reference filed 10/26/2007) is maintained. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1-3, 7 and 10 of U.S. Patent No. 6,617,135 B1 are drawn to a fusion protein comprising a first polypeptide chain comprising an immunoglobulin region and a first subunit of

IL-12 (p35 or p40) and a second polypeptide chain comprising a cytokine and a second subunit of IL-12 (p40 or p35), wherein the cytokine is a four-helix bundle protein, wherein the first and second polypeptides are covalently bonded by a disulfide bond. Claims 1-3, 7 and 10 of U.S. Patent No. 6,617,135 B1 do not specifically teach wherein the antibody comprises the heavy and light chain variable regions of the BC1 antibody or wherein the antibody is the BC1 antibody, or a humanized BC1 antibody. These deficiencies are made up for in the teachings of Mariani et al and Gillies et al [a].

Mariani et al have been described supra.

Gillies et al [a] have been described supra.

The claims in the instant application are obvious variants of claims 1-3, 7 and 10 of U.S. Patent No. 6,617,135 B1 because it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of claims 1-3, 7 and 10 of U.S. Patent No. 6,617,135 B1 and Mariani et al and Gillies et al [a].

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of claims 1-3, 7 and 10 of U.S. Patent No. 6,617,135 B1 and Mariani et al and Gillies et al [a] because Mariani et al teach monoclonal antibody BC1 that binds human oncofetal fibronectin, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues and radiolabeled BC-1 showed favorable tumor targeting *in vivo* and Gillies et al [a] teach antitumor antibody-IL-12 fusion proteins comprising human p35 and p40 domains that induce active antitumor immune responses within the tumor microenvironment and provides an important alternative to systemic IL-12 administration or gene therapy for increasing its therapeutic index, wherein the antibody-IL-12 fusion proteins include whole antibody-IL-12, humanized antibody-IL-12 and scFv-IL-12. Therefore, one of ordinary skill in the art at the time the invention was

made would have been motivated to increase the therapeutic index of IL-12 by targeting IL-12 within the tumor microenvironment for inducing antitumor immune responses and one of ordinary skill in the art would have been motivated to target human oncofetal fibronectin, which has extremely restricted distribution in normal adult tissues and is highly expressed in tumor tissues using the BC1 antibody or antigen-binding region thereof (e.g., scFv), or humanized BC1 antibodies. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced BC1-IL-12, humanized BC1-IL-12 and BC1 antigen-binding fragment-IL-12 fusion proteins (e.g., BC1scFv-IL-12) comprising the human IL-12p35 and IL-12p40 domains for therapeutic benefit in cancer patients in view of claims 1-3, 7 and 10 of U.S. Patent No. 6,617,135 B1 and Mariani et al and Gillies et al [a].

Claims 1, 4-7, 11-27, 34, 43-44, 53-54 and 57-58 are directed to an invention not patentably distinct from claims 1-3, 7 and 10 of commonly assigned U.S. Patent No. 6,617,135 B1. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,617,135 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments

Applicant argues as above against the obviousness rejections, i.e., one of ordinary skill in the art would not have been motivated to target IL-12 to a non-ED-B domain and targeting the non-EB-D region confers unexpected advantages and the examiner's remarks above apply here as well and are incorporated by reference. Thus, applicants' arguments are not found persuasive and the rejections are maintained.

Claim Objections

24. Claim 54 is objected to in the recitation "humanized murine BC1 antibody". Consider, amending the claim to recite "humanized BC1 antibody".

Appropriate correction is required.

25. No claim is allowed.

26. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with

alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643